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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,093	DALY, JOHN	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44 and 46-102* is/are pending in the application.

4a) Of the above claim(s) *1-22,29,43,59-67,69-84 and 103-106* is/are withdrawn from consideration.

5)☒ Claim(s) *68* is/are allowed.

6)☒ Claim(s) *23-25, 27, 28, 30-36, 38-42, 44, 46-57, 85-97, 99, 102* is/are rejected.

7)☒ Claim(s) *26,37,58,98,100 and 101* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 2/22/05. Claim 45 has been cancelled. Claims 23, 28, 41, 44, 46 and 49 have been amended. Claims 1-44 and 46-106 are pending in this application. Claims 1-22, 29, 43, 59-67, 69-84 and 103-106 have been withdrawn. Therefore, claims 23-28, 30-42, 44, 46-58, 68 and 85-102 are under examination in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and, therefore, this action is final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-25, 27, 28, 30-36, 39, 40-42, 44, 46-48, 50-57, 85-97, 99 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorens et al (US 2004/0002056; see entire document) in view of Shyu et al (Genes and Development, 1989, Vol 3, pages 60-72; see entire document) or Giordano et al (US 2004/0091866; see entire document). **This rejection is maintained for reasons of record in the office action mailed 12/16/04 and restated below based upon applicants' amendment.**

Applicants claim a construct comprising a polynucleotide that encodes a polypeptide with a protein-destabilizing element and a nucleic acid sequence that encodes a RNA element that modulates the stability of the transcript and a site for insertion of a gene expression-modulating element. The polynucleotide is not operable connected to a promoter.

Lorens et al teach use of self-inactivating vectors comprising reporter genes in methods of screening for candidate bioactive agents (see e.g. abstract). The vector comprises reporter constructs into which promoters are operably linked via an intron (see e.g. paragraph 0018-0020) as recited in part in claims 23, 24, 39, 40, and 85. The constructs are then used to identify agents that directly or indirectly regulate promoter activity (see e.g. paragraph 0013). As the vector is designed for the purpose of cloning promoters to analyze their activity, it has been designed without a promoter operably linked to the reporter. Paragraph 0018 supports this by teaching that the reporter is within the viral genome and the promoter is operably linked to it. To this end, the reporter gene comprises either PEST sequences or destruction boxes such that the reporter can more adequately serve as an indicator of real time events such as transcriptional activity (see e.g. paragraph 0020, 0130 and 0243) as recited in part in claims 27, 28, 87 and 91-95. Various promoters are inserted into the promoter as well as multiple promoters indicating that multiple cloning sites are required upstream of the reporter for insertion of heterologous promoters such as Eμ and 3' α E. As well, the polynucleotide encoding the reporter can be operably connected by use of a separation sequence to a selectable marker. Thus, the vector comprises polyadenylation sequences and selectable markers (see e.g. figure 4 and paragraph 0065) as recited in part in claims 25, 33-36, 41, 50-53, 96, 97, and 99. The reporter gene can be Renilla or firefly luciferase (see e.g. paragraph 0243 or 0016), light emitting reporter proteins as recited in

part in claims 30-32, 46-48, 88-90. Host cells include human cells (see e.g. paragraph 0153) as recited in claims 54-57 and 102.

Lorens et al do not teach inclusion of an RNA destabilizing element such as an AU rich element in the vector.

Shyu et al teach the generation of an expression vector comprising *c-fos* instability elements, ARE, which comprises SEQ ID NO:1 and SEQ ID NO:19 (see e.g. figure 1) and a second novel element within the *c-fos* protein coding region (See e.g. page 61, col 1, paragraph 2) as specifically recited in claim 44 and 86. The vector comprises the instability elements as a *c-fos*/β-globin fusion.

Giordano et al teach methods for identifying novel nucleic acid regulatory elements and compounds that affect regulation that can be used to effect regulation of a heterologous protein (see e.g. paragraph 0003). UTR sequences were inserted into cloning sites to assess for example sequences that affect the stability of the transcript such as destabilizing the transcript (see e.g. paragraph 0032).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add to the vector of Lorens et al the RNA destabilizing element taught by Shyu et al and Giordano et al because Lorens et al teach that it is within the ordinary skill of the art to generate a vector comprising a reporter gene with a protein degradation element for analysis of real time gene expression in cells and because Shyu et al and Giordano et al teach that it is within the ordinary skill of the art to include a RNA destabilizing element in a vector to regulate protein expression. One would have been motivated to do so in order to receive the expected benefit of decreased stability of the reporter mRNA to provide an indicator of dynamic cellular processes

such as transcriptional activity (see Lorens et al, paragraph 0130) by insertion of i.e. the c-fos AU rich element which results in rapid decay of the mRNA (see e.g. Shyu et al , page 61, col 1, paragraph 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorens et al (US 2004/0002056; see entire document) in view of Shyu et al (Genes and Development, 1989, Vol 3, pages 60-72; see entire document) or Giordano et al (US 2004/0091866; see entire document) further in view of Primig et al (Gene, 1998, Vol 215, pages 181-189; see entire document).

Applicants claim a construct comprising a chimeric gene comprising a coding sequence from a gene encoding a light emitting protein and a selectable marker protein and a nucleic acid sequence that encodes a RNA element that modulates the stability of a transcript encoded by the chimeric gene. The polynucleotide is not operable connected to a promoter. The polypeptide encoded by the polynucleotide is a chimeric gene such as comprising genes encoding light emitting protein and a selectable marker protein.

The teachings of Lorens et al and Shyu et al and Giordano et al are described above and are applied as before except:

Neither Lorens et al nor Shyu et al nor Giordano et al teach that the reporter is a chimeric gene encoding comprising genes encoding light emitting protein and a selectable marker protein.

Primig et al teach use of a reporter gene that is a fusion between GFP and neomycin phosphotransferase (see e.g. page 183, bridging paragraph col 1-2). The cited benefits of the

vector were localization of reporter and selection functions in one gene decreasing chances of undesirable recombination events, reducing false positives, optimal conditions for identifying gene expression modulators (see e.g. bridging paragraph page 187-188).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the separate reporter and selectable marker genes taught by Lorens et al in view of Shyu et al and Giordano et al with the GFP-neo fusion taught by Primig et al because Lorens et al in view of Shyu et al and Giordano et al teach that it is within the ordinary skill of the art to generate a vector comprising a reporter gene for analysis of gene expression in cells and because Primig et al teach that it is within the ordinary skill of the art to use GFP-neo as a reporter gene in cells. One would have been motivated to do so in order to receive the expected benefit of localization of reporter and selection function sin one gene decreasing chances of undesirable recombination events, reducing false positives, optimal conditions for identifying gene expression modulators (see Primig et al, bridging paragraph page 187-188). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorens et al (US 2004/0002056; see entire document) in view of Shyu et al (Genes and Development, 1989, Vol 3, pages 60-72; see entire document) or Giordano et al (US 2004/0091866; see entire document) further in view of Svensson and Akusjarvi (EMBO J. 1985, Vol 4, No. 4, pages 957-964; see entire document).

Applicants claim a construct comprising a polynucleotide and a nucleic acid that encodes an RNA element that modulates stability of a transcript and a site for introducing a gene expression-modulating element and a translational enhancer.

The teachings of Lorens et al and Shyu et al and Giordano et al are described above and are applied as before except:

Neither Lorens et al nor Shyu et al nor Giordano et al teach that the vector further comprises a translational enhancer.

Svensson and Akusjarvi teach the use of adenovirus VA RNAI on the translation of mRNAs. The expression was elevated 2-6 fold (see e.g. abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add to the vector of Giordano et al or Lorens et al in view of Shyu et al and Giordano et al the VA RNAI translation enhancer taught by Svensson and Akusjarvi because Lorens et al in view of Shyu et al and Giordano et al teach that it is within the ordinary skill of the art to generate a vector comprising a reporter gene for analysis of gene expression in cells and because Svensson and Akusjarvi teach that it is within the ordinary skill of the art to include a translational enhancer in a vector. One would have been motivated to do so in order to receive the expected benefit of enhanced reporter activity to identify low signaling events or elements that modulate these events. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 103(a) on pages 21-24 of the amendment filed 2/22/05. Applicants argue that neither the methods of Shyu et al nor of Giordano et al teach or suggest use of RNA destabilizing elements to assay transcriptional activity or for determination of real-time transcriptional activity. Rather the use of RNA destabilizing elements to decrease the stability of reporter gene mRNA for real time determination of changes in gene expression was first taught by the instant application. Furthermore, applicants argue that none of the references teach use of a vector in which the reporter gene is not operably linked to a promoter.

Applicants' arguments filed 2/22/05 have been fully considered but they are not persuasive. The MPEP teaches, "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." (see MPEP 2143.01). In the instant case, Lorens et al teach use of a reporter that has a protein instability sequence for decreased stability of the reporter mRNA to provide an indicator if dynamic cellular processes such as transcriptional activity (see Lorens et al, paragraph 0130). Shyu and Giordano et al teach insertion of an RNA instability sequence into heterologous sequences for decreased stability of the heterologous sequence. Giordano et al teach that this sequence can be specifically used to alter or control expression of the coding region of a heterologous protein (see e.g. paragraph 0073). Therefore, the motivation to combine the references to arrive at the claimed invention is in the "nature of the problem to be solved" because each reference was directed to the same problem of controlling expression of a coding region especially that of a heterologous protein.

Lorens et al furthermore teaches a SIN vector in which a reporter gene is inserted into a SIN vector. The construct is established for the insertion of a variety of promoters to analyze the effect of compounds upon the promoter. To this end, it appears from the description in the specification that the reporter is a part of the vector and the promoters are inserted into the vector. In this case, as in the instant application, the vector comprises a reporter with a cloning site for insertion of promoters.

Conclusion

Claim 68 is allowed.

Claims 26, 37, 58, 98, 100 and 101 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 23-25, 27, 28, 30-36, 38-42, 44, 46-57, 85-97, 99 and 102 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

May 4, 2005

GERRY LEFFERS
PRIMARY EXAMINER